Late outcomes in patients with uncorrected mild to moderate mitral regurgitation at the time of isolated coronary artery bypass grafting

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Objectives: Patients undergoing coronary artery bypass grafting often have untreated mild to moderate mitral regurgitation. The long-term outcome of these patients follows an uncertain course. The purpose of this study was to examine the late outcomes in patients with mild to moderate mitral regurgitation at the time of isolated coronary artery bypass grafting.

Methods: One hundred sixty-three patients with mild to moderate mitral regurgitation at the time of isolated coronary artery bypass grafting were identified from the prospectively collected cardiovascular database at Sunnybrook and Women's College Health Sciences Centre. These patients were matched 1:2 with patients who had isolated coronary artery bypass grafting without mitral regurgitation according to gender, age, left ventricular ejection fraction, New York Heart Association functional class, vascular disease, diabetes, extent of coronary disease, and year of surgery. There was 99% complete follow-up. Actuarial survival and event-free (death, myocardial infarction, stroke, cardiac hospitalization, and cardiac reintervention) survivals were compared by log-rank methods. Cox regression was used to assess the effects of the presence of mitral regurgitation on late survival and event-free survival. Preliminary postoperative follow-up echocardiography was available for 49 of the 163 patients with mitral regurgitation.

Results: There were 489 patients in the matched-cohort study, 163 with mitral regurgitation and 326 without. The average length of follow-up was 3.37 ± 2.04 years. There was no difference in actuarial survival at 6 postoperative years (mitral regurgitation 81.0% vs no mitral regurgitation 84.7%, $P = .9185$). Event-free survival at 6 years was worse in the mitral regurgitation group (45.7% vs no mitral regurgitation 64.7%, $P = .0258$) . Patients with mitral regurgitation had worse functional status (New York Heart Association class 3-4 20.0%, n = 30/150, vs no mitral regurgitation 8.1%, n = 25/307, $P = .0046$). After the matched variables were controlled for, the hazard ratios associated

with the presence of mitral regurgitation by Cox regression were 0.958 (P = .7626) for survival and 1.198 (P = .0333) for event-free survival. The only other significant predictor of late survival was preoperative intra-aortic balloon pump insertion (hazard ratio 2.484, P = .0365). Of the patients who underwent follow-up echocardiography, 30.6% (n = 15/49) had progression of mitral regurgitation to moderate to severe degree at an average of 16.4 postoperative months.

Conclusion: Overall late survival was not affected by the presence of mild to moderate degrees of mitral regurgitation in patients undergoing coronary artery bypass grafting. However, these patients had poorer event-free survival and worse late functional status. In a subset of patients with echocardiographic follow-up, the postoperative course of mitral regurgitation was variable, and nearly a third of these patients had worsening mitral regurgitation. Consideration should be given to repairing moderate mitral regurgitation in selected cases to improve long-term quality of life.

A significant proportion of patients undergoing surgical management of coronary artery disease have concomitant mitral regurgitation (MR).[1] It has been previously shown that 5% to 8% of patients undergoing coronary catheterization have some degree of MR[2]. The presence of even mild MR has been shown to influence late survival after acute myocardial infarction.[3] Among patients with MR after acute myocardial infarction, it has been shown that most have only mild MR on echocardiography.[4]. The 1-year survival of these patients is much worse than that of those without MR, with only 83% of patients with MR alive at 1 year after infarction, versus 94% of those without MR.[5].

Current American Heart Association guidelines are available for severe MR and concomitant coronary artery bypass grafting (CABG), and few surgeons address mild or moderate MR at the time of CABG, mainly because the addition of a mitral valve procedure at the time of CABG increases the risk of surgery.[6] Many surgeons prefer to treat MR complicating ischemic heart disease with isolated CABG alone. In fact, evidence from Emory University has demonstrated that this may be an acceptable option, with a reported survival of 77% at 5 years among patients with moderate ischemic MR treated with isolated CABG.[7] A follow-up comparison study of these patients compared with a matched cohort without MR also undergoing CABG showed no differences in late survival as late as 10 years after the surgery.[8] However, there is conflicting evidence that moderate MR in patients undergoing CABG only is associated with worse long-term outcome.[9] Aklog and colleagues[10] have reported that CABG alone for moderate ischemic MR leaves many patients with significant residual MR. Because of these conflicting data, this study was undertaken to examine the early and late outcomes in patients with ischemic heart disease and MR of degree 1+ to 2+ on preoperative angiography treated with isolated CABG at Sunnybrook and Women's College Health Sciences Centre.

Methods

Study Population

From January 1, 1994, to June 30, 2002, a total of 6443 patients underwent isolated CABG at Sunnybrook and Women's College Health Sciences Centre. Data were prospectively collected on more than 250 demographic, operative, and outcome variables of these patients and entered into the divisional research database at the institution. From the database, 163 patients were found to have undergone surgery with evidence of 1+ to 2+ MR on preoperative left ventricular angiography. This corresponds with mild to moderate degrees of MR.[11] Where a left ventricular angiogram was absent, preoperative echocardiogram data was used to determine the presence of MR. This was done for 8/163 patients. All these patients had functional MR on preoperative echocardiography of mild to moderate degree (2+ to 3+). All identified patients were included in the study, thus, representing a consecutive series of 163 patients with mild to moderate MR undergoing isolated CABG.

These patients were matched 1:2 (n = 326) with patients undergoing isolated CABG without the presence of MR. The 9 variables chosen for matching were age, gender, the presence of diabetes mellitus (both type I and type II), extent of coronary artery disease (single, double, or triple vessel disease), left ventricular grade (grade 1 left ventricular ejection fraction [LVEF] >60%, grade 2 LVEF 40%-60%, grade 3 LVEF 20%-40%, grade 4 LVEF <20%), timing of surgery (elective, urgent, or emergency), preoperative New York Heart Association (NYHA) functional class, the presence of renal dysfunction (normal vs dialysis dependent or preoperative serum creatinine >150 μmol/L), and year of operation.

Follow-up

Follow-up information was obtained for 94% of patients with MR (n = 147/157) and 95% of patients without MR (n = 301/317).

TABLE 1. Patient demographic data

Characteristic	No MR, entire cohort (n = 6236)	No MR, matched group (n = 326)	MR study group (n = 163)	*P* value*
Age (y, mean ± SD)	63 ± 10	65 ± 10	66 ± 10	<.0001
Age >70 y (%)	29.5%	45.7%	45.7%	<.0001
Female (%)	22.7%	34.2%	34.2%	<.0001
Diabetes mellitus (%)	24.7%	22.6%	22.6%	.2394
Peripheral vascular or cerebrovascular disease (%)	20.8%	22.2%	23.2%	.1223
Renal dysfunction (%)	2.8%	4.9%	4.9%	.0012
Chronic obstructive pulmonary disease (%)	4.9%	5.2%	5.5%	.3455
Left ventricular grade 3–4 (%)	20.3%	44.5%	44.5%	<.0001
NYHA functional class 3–4 (%)	23.5%	89.0%	89.0%	<.0001
Recent myocardial infarction (%)	8.3%	18.3%	16.3%	<.0001
Disease extent (%)				<.0001
Single-vessel disease	6.0%	2.5%	1.2%	
Double-vessel disease	27.3%	22.5%	23.8%	
Triple-vessel disease	66.7%	75.0%	75.0%	
Left main disease	35.1%	24.4%	24.4%	

*Values shown are for MR study group versus patients without MR in the entire cohort. Comparisons of MR study group versus matched group without MR did not reach significance because of matching selection.

TABLE 2. Operative data: Comparison of patients undergoing CABG with and without mild to moderate MR

	No MR (n = 326)	MR (n = 163)	*P* value
No. of grafts (mean ± SD)	3.21 ± 0.90	3.38 ± 0.76	.5767
Arterial grafts (mean ± SD)	1.30 ± 0.73	1.24 ± 0.73	.5556
Internal thoracic artery use (%)	91.1%	89.0%	.4672
Crossclamp time (min, mean ± SD)	79 ± 32	73 ± 26	.001
Cardiopulmonary bypass time (min, mean ± SD)	103 ± 41	92 ± 28	.001
Incomplete revascularization (%)	12.3%	14.0%	.5927
Mortality (%)	2.8%	3.5%	.8611
Perioperative myocardial infarction (%)	1.8%	4.0%	.2027
Stroke (%)	2.4%	4.0%	.3737
Low output syndrome/intra-aortic balloon pump (%)	14.6%	17.5%	.2718

This information was supplemented with data from provincial health card information to determine mortality among patients who could not be contacted. This procedure resulted in a total of 99% complete follow-up information for survival data. There were 2 patients without MR and 3 patients with MR who were unavailable for follow-up. These cases were treated in each of three ways with respect to future analyses: (1) they were treated as missing values, (2) they were treated as events, and (3) they were treated as nonevents. The final results of the analyses were not significantly different depending on the statistical management of these patients; thus for consistency, these patients are always treated as missing in the analyses presented here.

Statistical Analysis

All analyses were performed with SAS version 8.0 (SAS Institute, Inc, Cary, NC) for Microsoft Windows XP operating system (Microsoft Corporation, Redmond, Wash) on a desktop computer system. Continuous data were compared with 2-tailed paired Student *t* tests; categoric data were analyzed with χ^2 or Fisher exact statistics. Conditional maximum likelihood estimation of parameters was used to obtain estimates of odds ratios for risk factors for perioperative events. Survival data were compared with log-rank methods, and proportional hazards analyses were used for multivariable adjustment of late outcomes.

Results

Table 1 shows the demographic characteristics of patients with mild to moderate MR compared with a concurrent group of patients from the same period undergoing isolated CABG with no MR. The patients with MR were older, more likely to be female, had a higher incidence of renal dysfunction, had poorer ventricular function and preoperative functional status, and had a higher incidence of triple-vessel disease than patients without MR. The preoperative characteristics shown in Table 1 were used to match the study cohort.

The operative results and data are shown in Table 2, comparing patients with CABG and mild to moderate MR (n = 163) with the group of matched patients undergoing CABG without MR (n = 326). It can be observed from this table that in terms of basic perioperative data and early postoperative results, no significant differences were found between patients with MR and those matched patients without MR.

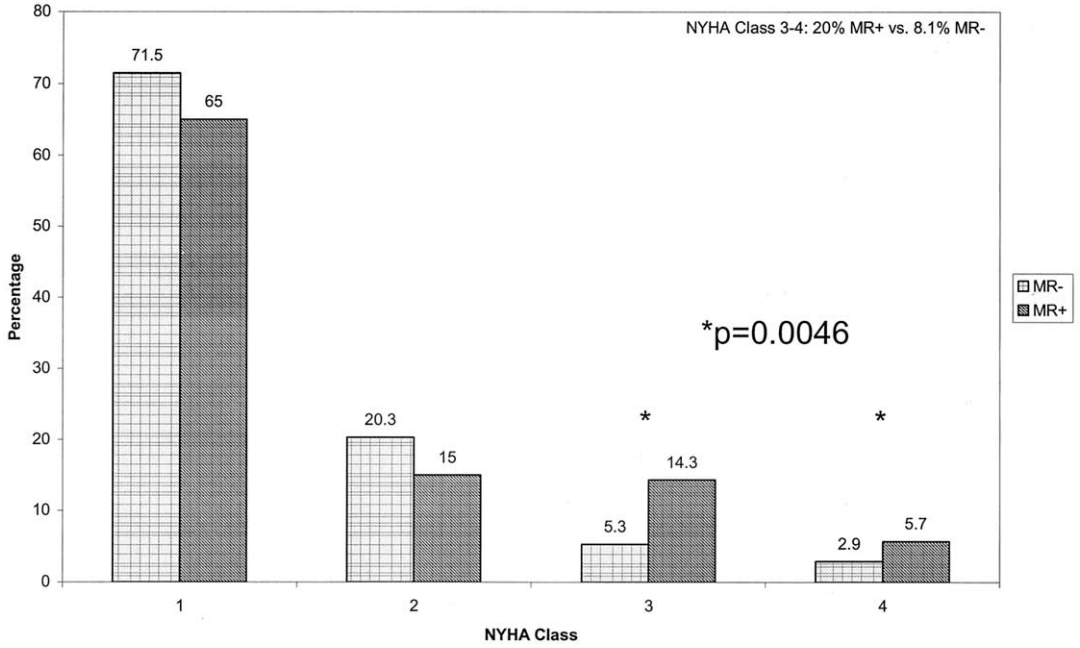

Figure 1. Late functional status. Patients with mild to moderate MR *(MR+)* at isolated CABG had poorer late functional status than those without *(MR−).* Twenty percent of patients with MR were in late NYHA functional class 3 or 4, compared with 8.2% of patients without MR ($P = .0046$).

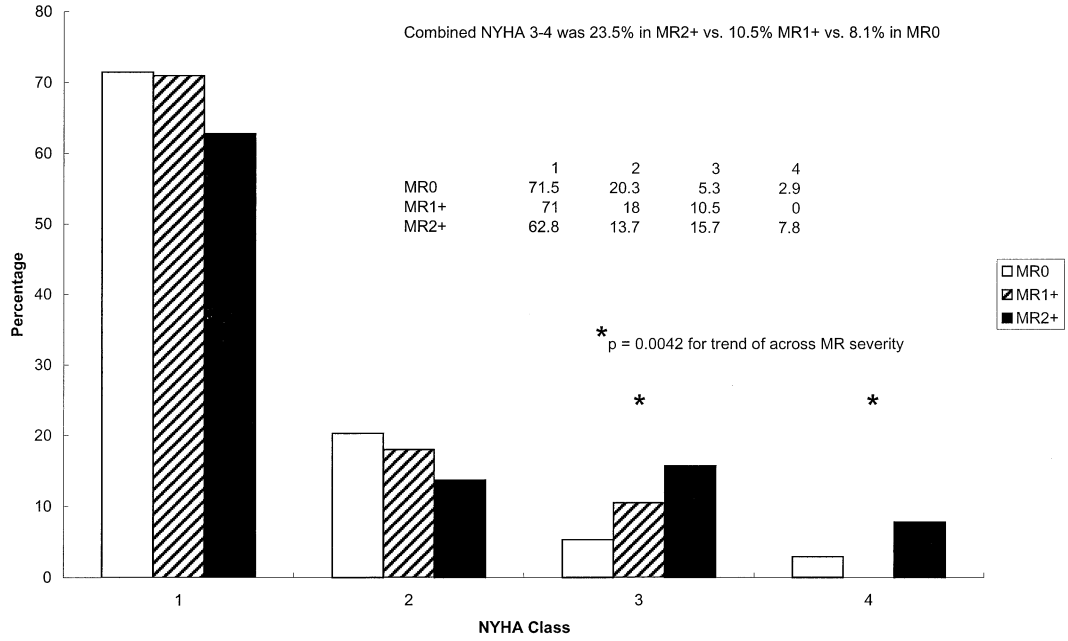

Figure 2. Late functional status by severity of MR. Increasing degree of MR at isolated CABG was associated with trend toward increasing late NYHA functional class ($P = .0042$).

Figures 1 and 2 demonstrate the late functional status of patients in both groups. In Figure 1, patients with MR had a higher incidence of NYHA functional class 3 or 4 than do patients without MR (20.0% vs 8.1%, $P = .0046$) at a mean follow-up of 3.4 ± 2.0 years. When analyzed by actual degree of MR, as shown in Figure 2, an increase in NYHA

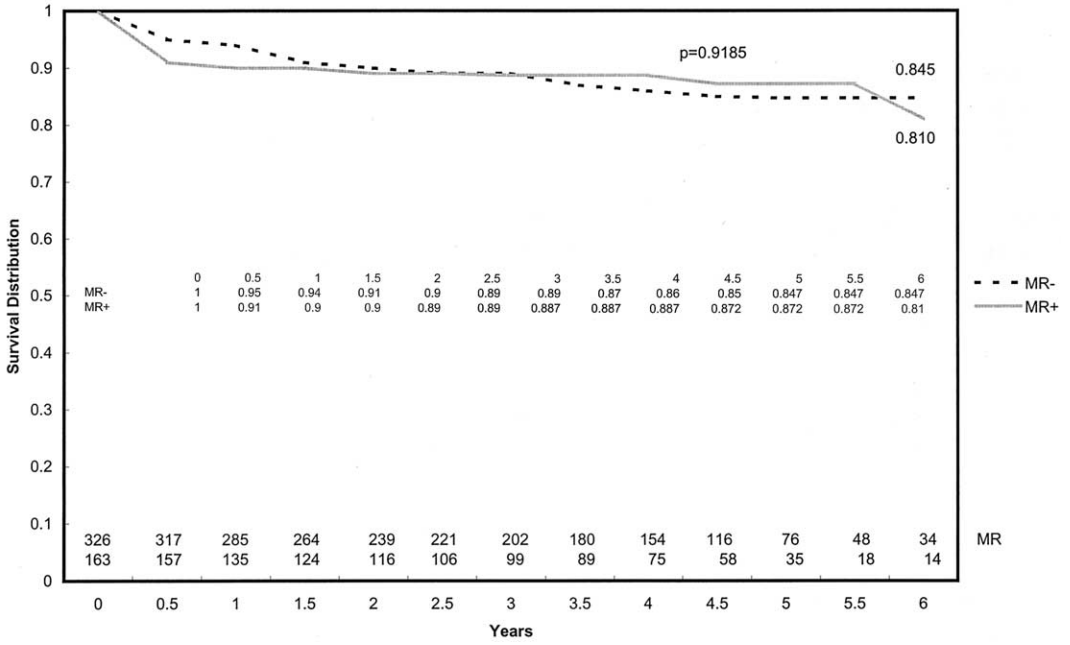

Figure 3. Late survival. There was no difference in late survival (mean follow-up 3.4 ± 2.0 years) between groups with *(MR+)* and without *(MR−)* MR as late as 6 years after surgery.

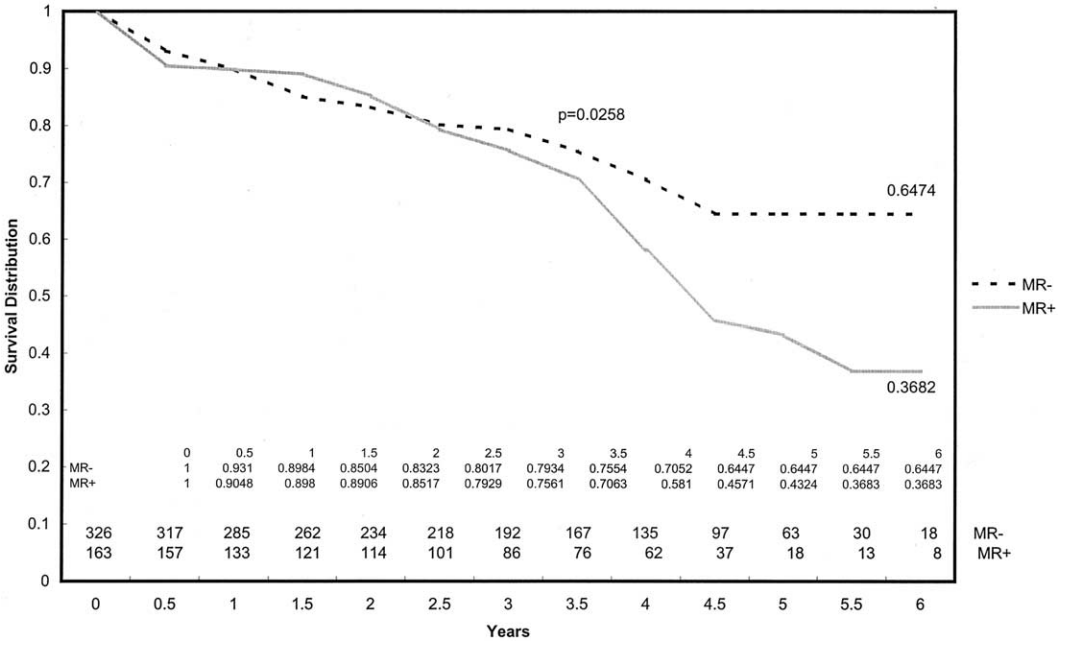

Figure 4. Late event-free survival. There was better late event-free survival among patients without MR *(MR−)* at isolated CABG. Event-free survival was 64.7% in patients without MR, compared with 36.8% in patients with MR (*MR+*, *P* = .0258).

class was observed as the degree of MR increased from absent (MR0, 8.1%) to mild (MR1, 10.5%) to moderate (MR2, 23.5%, $P = .0042$).

Overall patient survival, as shown in Figure 3, was found to be similar in patients with MR and without MR at late follow-up. Patients with MR had a 6-year survival of 81.0%,

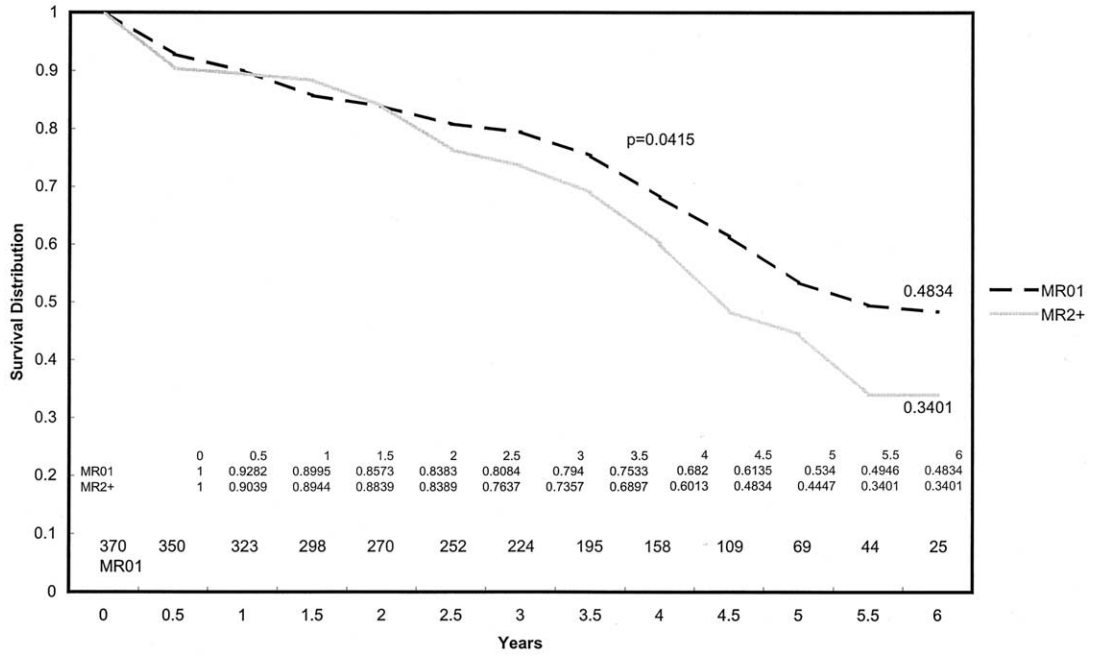

Figure 5. Late event-free survival by severity of MR. Patients with 2+ MR had significantly worse late event-free survival than did patients with either absent MR or 1+ MR combined (34.0% vs 48.3%, $P = .0415$).

versus 84.5% among patients without MR ($P = .9185$). Survival of the overall patient cohort of patients undergoing isolated CABG during the same period as the study patients was significantly better at 6 years (90.7%, $P = .0001$) than the survival of either subgroup (Figure 3), reflecting the presence of important comorbidities.

The late event-free survivals are shown in Figures 4 and 5. Figure 4 shows event-free survival to be much worse in patients with MR (36.8%) than in a matched cohort of patients without MR (64.7%, $P = .0258$). In Figure 5, patients with mild MR (n = 44) were included with the patients without MR (n = 370 total); the event-free survival of patients with moderate MR (n = 119) was significantly worse (MR2 34.0% vs MR01 48.4%, $P = .0415$). When survival was analyzed by individual MR severity, a trend toward a significant difference in event-free survival was observed for mild (44.7%) versus moderate MR (34.0%, $P = .0745$).

Cox regression was used to determine the effect of MR severity on late survival and event-free survival. The hazard ratios associated with the presence of MR were 0.958 ($P = .7626$) for overall survival and 1.198 ($P = .0333$) for event-free survival. Thus the presence of mild to moderate MR was not significantly associated with poorer overall survival but was significant in predicting poorer event-free survival.

The causes for late hospitalization are shown in Table 3.

TABLE 3. Causes of hospitalization in follow-up of patients with or without MR after isolated CABG

	No MR (n = 281)		MR (n = 138)	
Reason for admission	**No.**	**%**	**No.**	**%**
No hospitalization	260	92.5	111	80.4
Congestive heart failure	5	1.8	16	11.6
Atrial fibrillation	2	0.7	1	0.7
Amputation	0	0	2	1.5
Unstable angina pectoris	3	1.1	4	2.9
Myocardial infarction	0	0	3	2.17
Stroke	1	0.4	1	0.7
Deep venous thrombosis	1	0.4	0	0
Pneumonia	5	1.8	0	0
Peripheral vascular disease	1	0.4	0	0
Syncope	3	1.1	0	0

Of the patients with MR, 80.4% had no hospitalization during follow-up, compared with 92.5% of patients without MR. The increased rate of hospitalization seen in patients with MR could be accounted for by the higher incidence of congestive heart failure (11.6% with MR vs 1.8% without, odds ratio 7.14, $P < .0001$). Other causes for late hospitalization in both groups included atrial fibrillation, amputation for peripheral vascular ischemia, angina, myocardial infarction, deep venous thrombosis, pneumonia, stroke, syncope, and intermittent claudication.

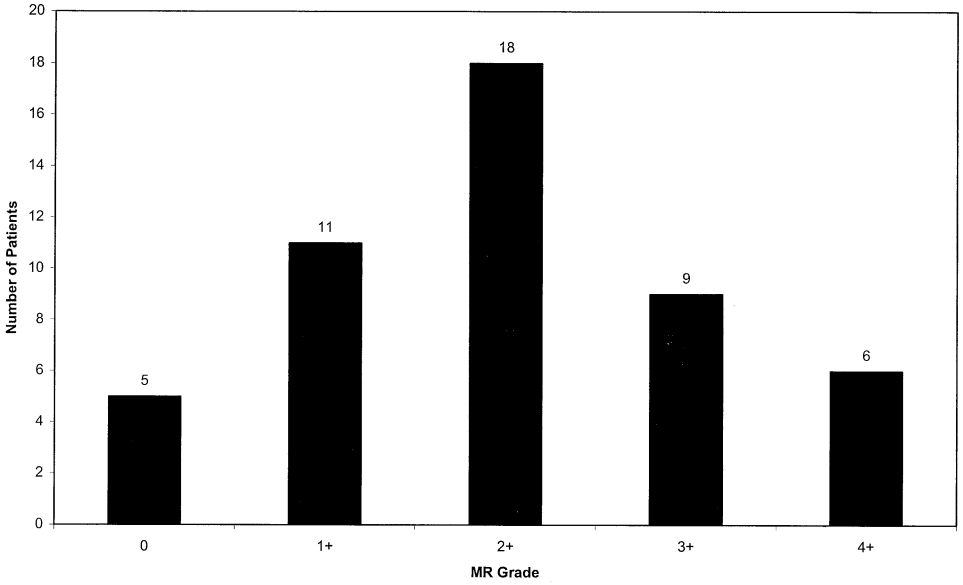

Figure 6. Degree of MR on follow-up echocardiography. Postoperative echocardiograms were available for 49 patients with evidence of mild to moderate MR at isolated CABG. Of these, 15 (30.6%) had moderate to severe MR at follow-up echocardiography. Mean follow-up time was 16.2 ± 20.5 months.

Follow-up echocardiography was performed in 49 cases in the MR group at a mean of 16.2 ± 20.5 postoperative months. The results of these follow-up studies are shown in Figure 6. Among the 49 patients tested, 30.6% (n = 15) showed progression to moderate to severe MR at the time of the follow-up study. Of the 15 patients with moderate to severe MR on late echocardiography, 47% (n = 7) had required hospitalization for congestive heart failure, compared with 2.9% (n = 1) of the 34 patients with mild (or less) MR ($P < .0001$)

Discussion

Traditionally, patients with mild to moderate MR have not been considered for combined mitral valve repair and CABG. The finding of 1+ to 2+ MR when viewing a preoperative angiogram in patients with a history of myocardial infarction and depressed ventricular function has been considered incidental, without much influence on late patient outcomes. This study was born of an uncertainty with respect to the management of these patients. There is a lack of evidence in the literature addressing the late outcomes in patients with incidental findings of MR on ventriculography.

The Society of Thoracic Surgeons database collects information on the results of surgery after various procedures from participating centers across North America. The risk for increased morbidity and mortality of surgery after combined CABG and mitral repair procedures is approximately twice the risk after isolated CABG. However, these results include patients undergoing emergency procedures for acute MR. In addition, patients with severe MR are included in the cohort. Despite these concerns, most surgeons consider the risk of a combined procedure too high for what is considered a relatively benign finding of mild to moderate MR.

Literature does exist on the survival of patients with moderate (3+ on echocardiography) MR undergoing isolated CABG, as well as combined mitral valve repair and coronary surgery. Aklog and colleagues[10] have shown that in patients with moderate ischemic MR, treatment with isolated CABG alone results in significant residual MR. Furthermore, their data from 38 patients with established 3+ ischemic MR on preoperative assessment who also underwent intraoperative transesophageal echocardiography suggested a significant risk of underestimation of the degree of MR solely from intraoperative assessment.

The Emory University group has reported on a cohort of 58 patients operated on between 1977 and 1983 at 5 and 10 years of follow-up. These patients all had moderate MR, and the group was not able to demonstrate a significant difference in survival between patients with and without MR treated with isolated CABG. Significantly, the cohort of patients being reported on were slightly younger than those in this study (63 years vs 66 years) and had significantly better preoperative functional status, with only 10% of patients in NYHA class 3 or 4 versus 89% in his study. Data were not given with respect to the late functional status of these patients, nor to freedom from cardiovascular related morbidity in follow-up.[7,8]

In a recent study from Yale,[12] patients with severe ventricular dysfunction and mild to moderate (1+ to 3+ on preoperative echocardiography) MR treated with isolated CABG had marked improvement in postoperative ventricular function with a decrease in MR. The degree of MR had decreased from 1.73 to 0.54 at a mean of approximately 3 years after the operation. The mean NYHA class improved from 3.3 to 1.8. The average preoperative LVEF in these patients was only 22%. These patients may represent an extreme in terms of cardiovascular risk; the 5-year survival of 50% suggests that these are indeed very ill patients.

In studies from Cedars-Sinai Hospital,[9] a combined suture mitral annuloplasty and CABG in patients with moderate ischemic MR resulted in significant improvement in MR after the operation relative to treatment with CABG alone. However, there was no difference in overall late survival between treatment arms, and there was a high incidence of late failure of the suture annuloplasty to control MR, with 25% of patients with suture annuloplasty having significant MR on late follow-up.

Prifti and associates[13] reported on a study of 99 patients with mild or moderate ischemic MR grouped into four treatment arms. The 3-year cumulative mortality among patients with moderate MR treated with CABG alone was 59%, significantly higher than that among patients with moderate MR treated with CABG and mitral repair or among patients with only mild degrees of MR whether treated with CABG alone or with a combined procedure. This study also showed that there was a significant increase in mortality from adding simple annuloplasty repairs to patients undergoing coronary surgery.

In our study, overall survival among these patients was not affected by the presence of MR when compared with a matched cohort of patients without MR. However, the late event-free survival and late functional status were significantly poorer in patients with MR. Twenty percent of patients with MR are in NYHA functional class 3 or 4 in late follow-up, compared with only 8.1% of patients without MR. When only patients with 2+ MR on preoperative ventriculography are included in the analyses, the incidence of poor late functional status is 23.5%.

A closer examination of the reasons for late hospitalization reveals that untreated MR at the time of isolated CABG results in a significantly higher incidence of hospitalization for congestive heart failure, atrial fibrillation, syncope, and stroke. The significant difference in late event-free survival seen in patients with MR treated by CABG alone can be accounted for by the increased incidence of congestive heart failure in these patients. Late echocardiography demonstrated that of 8 patients admitted for congestive heart failure, 87.5% ($n = 7$) had moderate to severe MR. Thus it would appear that the presence of mild to moderate MR on preoperative ventriculography is not simply an incidental finding but one that may have a significant impact on late functional status and quality of life.

What should the operative strategy be for these patients? The goal of surgical therapy is not only to improve late survival but also to improve late functional status and late quality of life. However, these goals should be achieved without increasing perioperative morbidity and mortality. An appropriate strategy for the management of 1+ to 2+ MR discovered on preoperative ventriculography should be to first establish the degree of MR by preoperative echocardiographic assessment of the mitral valve apparatus. If a patients is found to have only a trivial or mild degree of MR on preoperative echocardiography, then that patients should be treated with isolated CABG. If a moderate or severe degree of MR is established by preoperative echocardiographic assessment, however, then the patient should be considered for mitral valve repair. This data suggests that low-risk patients with moderate MR should strongly be considered for combined mitral valve repair and CABG if this can be accomplished without an increase in operative morbidity or mortality.

Limitations of this study include its nature as a retrospective matched cohort analysis. Although techniques of multivariable analysis may adequately control for measurable biases, unmeasured bias may still have a strong influence on the presented results. Another limitation of this study is the question on which it was based. The criterion standard for assessment of mitral valve disease is preoperative echocardiography; however, the problem presented in this article is what is commonly encountered in clinical practice. Patients are often referred for isolated CABG when only a coronary angiogram and left ventriculogram have been performed. The purpose of this study was to determine the outcomes in patients with an incidental finding of mild to moderate MR on left ventriculography.

It should be noted that this study does not prove that adding a mitral valve procedure at the time of isolated CABG to treated concurrent mild to moderate MR is beneficial. What is needed is a study, preferably a randomized clinical trial, that could compare the treatment algorithms of isolated CABG and CABG with mitral valve procedure.

In conclusion, patients with mild to moderate degrees of MR on preoperative ventriculography have a similar overall survival to patients without MR but a poorer event-free survival, poorer late functional status, and higher incidence of hospitalization for congestive heart failure. The finding of mild to moderate MR therefore should not be treated as an incidental finding but should be further evaluated with preoperative echocardiographic assessment. The nature and degree of MR, as well as the patient risk profile, should guide the further management of these patients.

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Discussion

Dr Frank W. Sellke *(Boston, Mass).* With patients with moderate MR, I tend to fix it if they have symptoms related to congestive heart failure and leave it alone if they don't have symptoms related to congestive heart failure. Do you think that is a reasonable approach? How do you decide whether to repair the MR at the time of surgery?

Dr Mallidi. As you can see from our study, 90% of the patients in this study had heart failure symptoms.

Dr Sellke. At the time of surgery?

Dr Mallidi. At the time of surgery or within 1 month before surgery. So I think one way that you can interpret the study is that for patients who have heart failure and have moderate MR but are maybe at high risk for other reasons, such as low LVEF or some other reason, you can look at the study and say that these patients do fairly well in the late follow-up with isolated CABG. On the other hand, if you have a low-risk patient with symptoms of heart failure and moderate MR, then perhaps it might be worthwhile to consider a mitral valve repair.

Dr Sellke. How about somebody with mild MR with shortness of breath; would you fix that?

Dr Mallidi. No.

Dr Robert A. Dion *(Leiden, The Netherlands).* In this category of patients with fluctuating or intermittent MR, did you perform a dynamic test? We have been doing that for about 10 years now in our institution, and it helps distinguish between people that do not really need mitral valve repair and those who do. We do an intraoperative test with a filling test and an afterload test if we still have a doubt. Did you ever consider for this category of patient to use a dynamic test to see what happens with MR?

Dr Mallidi. Our study was mainly focused on the question of the patient referred for CABG who has mild to moderate MR when you look at the films. We certainly think that dynamic testing may be helpful in further or fully evaluating these patients to help determine whether you need to operate on the mitral valve, but none of these patients had that sort of testing.

Dr Hormoz Azar *(Norfolk, Va).* Excellent study, congratulations. Considering the divergence of the curves starting around 3.5 with symptoms, do you think that if these survival curves are carried longer that you are going to start seeing divergence in survival as well?

Dr Mallidi. That is an excellent question. Certainly we think that up to 6 years there was no difference in survival, but, as you mentioned, the symptoms started to develop 2 to 3 years after surgery, and this may result in late deaths or death between 5 and 10 years among patients with heart failure, most of whom had MR. So that is certainly a possibility.

Dr Ralph J. Damiano, Jr *(St Louis, Mo).* One of the weaknesses of the study is the fact that you used ventriculography, which is notoriously inaccurate in grading MR and often quite at variance with echocardiography. The other problem is that most of your follow-up is with echocardiography.

Do you have any data for the few patients for whom you had both echocardiography and ventriculography to show how accurate the preoperative ventriculogram was in grading the MR? I am interested in what percentage of patients actually had worsening with time. You may not have those data, but I think it is an interesting point that maybe would further support your hypothesis.

Dr Mallidi. We had preoperative echocardiographic and ventriculographic data available for about 35 patients. In those patients we continued to use the ventriculographic assessment for the purposes of the study, just to be consistent, but we did compare the findings of echocardiography and ventriculography. What we found was that among patients with 1+ or 2+ MR according to ventriculography, none of the patients had severe MR on echocardiography, and most of the patients had mild to moderate MR on echocardiography. However, a few patients had trivial or absent MR; out of the 35, I think there were 5 or 6 patients with absent or trivial MR. So we still would have included most patients in our study. It is absolutely true that a ventriculogram is not the best assessment. That is why of our first recommendation is that when you see this finding you should not ignore it, but investigate it with echocardiography.